A review of warfarin dosing and monitoring

MARIAMMA KURUVILLA, PHARMD, AND CHERYLE GURK-TURNER, RPH

The goal of anticoagulant therapy with warfarin is to administer the lowest effective dose of the drug to maintain the target international normalized ratio (INR). Warfarin, a vitamin K antagonist, is an oral anticoagulant indicated for the prevention and treatment of venous thrombosis and its extension and the prevention and treatment of the thromboembolic complications associated with atrial fibrillation. Warfarin has also been used to prevent recurrent transient ischemic attacks and to reduce the risk of recurrent myocardial infarction, but data supporting these indications are inconclusive at this time (1).

Warfarin inhibits the synthesis of clotting factors II, VII, IX, and X, as well as the naturally occurring endogenous anticoagulant proteins C and S (2). The anticoagulant and antithrombotic activity of warfarin depends on the clearance of functional clotting factors from the systemic circulation once the drug is administered (2, 3). The earliest changes in INR are typically seen 24 to 36 hours after administration of the dose. The antithrombotic effect of warfarin is not present until approximately the fifth day of therapy, which is dependent on the clearance of prothrombin (1, 2).

Initiation of warfarin therapy is challenging, since the pharmacodynamic response is delayed and difficult to predict. Because prothrombin has a half-life of around 50 hours, loading doses of warfarin are of limited value (4). In clinical practice, loading doses (e.g., 7.5 mg or more per day) of warfarin may increase the patient's risk of bleeding complications early in therapy by eliminating the production of functional factor VII (2, 5). Administration of loading doses may place a patient in a hypercoagulable state due to a severe depletion of protein C (2). The administration of a loading dose is a possible source of prolonged hospitalization secondary to dramatic rises in the INR value that may necessitate the administration of vitamin K (5). If a rapid anticoagulant effect is required, an initial dose of heparin or a low-molecular-weight heparin should be used and overlapped with warfarin for approximately 4 to 5 days. Once the INR is therapeutic for at least 2 days, the supplemental anticoagulation treatment may be discontinued (1, 4, 5).

The safety and efficacy of warfarin therapy are dependent on maintaining the INR within the target range for the indication *(Table 1)*. When a patient is started on an oral anticoagulant, INR monitoring should be performed daily until the INR is within the therapeutic range for at least 2 consecutive days. Unexpected fluctuations in the INR in an otherwise stable patient could be due to a change in diet, poor compliance, undisclosed drug use, alcohol consumption, or self-medication (2). Lab error should also be considered for unexpected values.

Table 1. Recommended therapeutic range for oral anticoagulant therapy*

Indication	INR
Treatment of venous thrombosis	2.0–3.0
Treatment of pulmonary embolism	2.0–3.0
Prophylaxis of venous thrombosis (high-risk surgery)	2.0–3.0
Prevention of systemic embolism	2.0–3.0
Tissue heart valves	2.0–3.0
AMI (to prevent systemic embolism)†	2.0–3.0
Valvular heart disease	2.0–3.0
Atrial fibrillation	2.0–3.0
Bileaflet mechanical valve in aortic position	2.0–3.0
Mechanical prosthetic valves (high risk)	2.5–3.5
Systemic recurrent emboli	2.5–3.5

*Adapted from reference 1.

†If oral anticoagulant therapy is elected to prevent recurrent myocardial infarction, an INR of 2.5 to 3.5 is recommended, consistent with recommendations of the Food and Drug Administration.

AMI indicates acute myocardial infarction; INR, international normalized ratio.

One of the major risks of warfarin therapy is bleeding, which correlates well with INR values. The Fifth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy has published guidelines on the management of patients with high INR values with or without bleeding *(Table 2)*.

WARFARIN DRUG UTILIZATION EVALUATION

Criteria for warfarin administration were developed that were supported by the medical literature and approved by the Drug Utilization Evaluation Subcommittee of the Pharmacy and Therapeutics Committee. A computer-generated report of all

From the Department of Pharmacy Services, Baylor University Medical Center, Dallas, Texas.

Corresponding author: Cheryle Gurk-Turner, RPh, Department of Pharmacy Services, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246 (e-mail: ck.turner@baylordallas.edu).

Table 2. Management of supratherapeutic INR values*

INR	Patient situation	Action
3.1–5.0	No bleeding or need for rapid reversal (i.e., no need for surgery)	Omit next few warfarin doses and/or restart at lower dose when INR approaches desired range. If the INR is only minimally above range, no dosage reduction may be required.
5.1–9.0	No bleeding or need for rapid reversal	Omit next 1–2 doses, monitor INR more frequently, and restart at lower dose when INR approaches target range or omit dose and give 1–2.5 mg vitamin K_1 orally (use this if patient has risk factor for bleeding).
	No bleeding but reversal needed for surgery or dental extraction within 24 hours	Vitamin K_1 2–4 mg orally (expected reversal within 24 hours); give additional 1–2 mg if INR remains high at 24 hours.
9.1–20.0	No bleeding	Stop warfarin; give vitamin K_1 3–5 mg orally; follow INR closely; repeat vitamin K_1 if needed. Reassess need and dose of warfarin when INR approaches desirable range.
Rapid reversal required (>20.0)	Serious bleeding or major warfarin overdose	Stop warfarin; give vitamin K_1 10 mg by slow IV infusion. May repeat vitamin K_1 every 12 hours and give fresh plasma transfusion or prothrombin complex concentrate as needed. When appropriate, heparin can be given until the patient becomes responsive to warfarin.
Life-threatening bleeding		Replace with prothrombin complex concentrate and give 10 mg of vitamin K_1 by infusion. May repeat if needed.

*From reference 1.

patients receiving warfarin was generated daily from July 24, 2000, to August 20, 2000. The information gathered was entered into Microsoft Access, and 50 patients were randomly selected to be included in the evaluation. A retrospective chart review was conducted for the patients identified through this randomized process. Descriptive and inferential statistics (chi-square, *t* test) were utilized for data analysis.

Overall, results identified 4 main variances related to warfarin therapy: 1) inappropriate administration of a warfarin loading dose, 2) inappropriate use of vitamin K, 3) inconsistent overlapping of heparin with warfarin, and 4) inconsistent provision of patient education.

Patients who are given a loading dose of warfarin often reach a supratherapeutic INR level that can place a patient at risk for bleeding and prolonged hospital stay. This complication has been attributed to excessive depression of factor VII and protein C (2, 5). The ACCP supports an "induction" dose (rather than a large loading dose) for initiation of therapy. This induction dose can range from 2 to 5 mg per day and is adjusted according to the patient's INR (1).

Inappropriate use of vitamin K can be improved by following the guidelines for dosing of vitamin K developed by the Fifth ACCP Consensus Conference on Antithrombotic Therapy (1). It is important to use vitamin K only when recommended, because inappropriate administration of vitamin K is associated with warfarin resistance. When such resistance develops, it is difficult to achieve a therapeutic INR in a timely manner, which may result in an increased risk of clotting events.

Another area of improvement relates to the practice of overlapping heparin with warfarin therapy. Heparin displays an anticoagulant effect within 1 day, while the anticoagulant effects of warfarin are not evident until the third day of therapy. If rapid anticoagulant effects are needed, heparin should be initiated first, and warfarin should be started within a day or two. The 2 drugs should be given concurrently until the INR value is within the therapeutic range (1–3).

Lastly, since warfarin has a narrow therapeutic window and has been associated with many drug-drug and drug-food interactions, patient counseling is crucial. The evaluation revealed this as an area for improvement because opportunities for patient education were not always optimized.

Initiation and management of warfarin therapy is often difficult. Guidelines have been developed to assist the clinician in determining target ranges for therapeutic success. In addition, strategies for rapid anticoagulation and management of supratherapeutic INR values are also described in the literature. Daily practice using these guidelines should make management of patients easier when warfarin therapy is required.

1. Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D, Brandt JT. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1998;114(5 Suppl):445S–469S.
2. Horton JD, Bushwick BM. Warfarin therapy: evolving strategies in anticoagulation. *Am Fam Physician* 1999;59:635–646.
3. Micromedex. Warfarin drug evaluations. Micromedex@Healthcare Series 2000;106.
4. Dager WE, Branch JM, King JH, White RH, Quan RS, Musallam NA, Albertson TE. Optimization of inpatient warfarin therapy: impact of daily consultation by a pharmacist-managed anticoagulation service. *Ann Pharmacother* 2000;34:567–572.
5. Lamb GC. Loading dose of warfarin. *JAMA* 1997;277:1196.